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Review Article

Deep brain stimulation modifies cognitive function

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ABSTRACT

The advent of brain stimulation techniques to treat movement disorders and psychiatric diseases has shown potential to decode the neural mechanism that underlies the cognitive process, by modulating the interrupted circuit. Given the increased interest in deciphering of the cognitive process, brain stimulation is under vigorous examination to explore its potential ability in facilitating cognitive function. Clinical studies involving brain stimulation have demonstrated increased cognition. Herein we summarize the cerebral circuits implicated in cognition and memory, and also proposed mechanisms that might underlie behavioral improvements after stimulation. Translational studies in animals and humans and technological advancements in bioengineering that expand the applicability of brain stimulation to ameliorate diseases with learning or memory impairment can be anticipated in the near future.

1. Introduction

Brain stimulation has become one of the major treatment choices for movement disorders and neuropsychiatric disorders, such as Parkinson's disease (PD), dystonia, and obsessive-compulsive disorders (OCDs). Most treatment effects have been based on suppression of either pathological electrophysiology (hyperactivity of the subthalamic nucleus in PD) or neuropsychiatric behaviors (obsessive thoughts and repetitive ritualized behaviors in OCD). Although the precise mechanism by which deep brain stimulation (DBS) exerts benefits is still elusive, increasing evidence suggests that it might involve multidisciplinary effects on the target where afferent nerves are stimulated, and neurotransmitters are released [1,2]. It is a prerequisite that these circuit neuromodulation effects all end up with restoration of disabling symptoms [3].

Recently, there have been several interesting studies in which scientists endeavored to enhance human cognitive function through various DBS targets with the aim of treating the most prevalent neurodegenerative diseases, such as Alzheimer's disease (AD) and diseases with memory impairment (Table 1) [4]. In this review, we highlight an up-to-date important target nucleus as well as connecting circuits that may provide insights into mechanisms underpinning how brain stimulation facilitates cognition and memory.

Memory is the process by which information is encoded, stored, and retrieved. Given the implicated functions of different cognitive processes, memory can be divided into declarative (explicit) and procedural (implicit) memory. In addition, declarative memory can be further subdivided into semantic memory, which relates knowledge of facts in the absence of memory for the context in which they are learned, and episodic memory, which is related to information specific to a particular context [5]. According to various requirements of cognitive function, we can anticipate that the neural underpinnings of these memories might involve different anatomical sites and circuits within the brain. These include limbic and diencephalic structures such as the hippocampus, amygdala, hypothalamus, and thalamus, and also the cortical and subcortical groups such as the medial prefrontal cortex and basal ganglia [6]. With their roles integrated into the formation of different kinds of memory, chemical or electrical stimulation targeting these structures may provide possibilities to boost cognitive function, some of which have been elucidated recently (Fig. 1).

2. Brain stimulation and cognition improvement: Clinical evidence

2.1. Entorhinal cortex stimulation facilitates spatial memory

Traditionally, medial temporal structures have been correlated with memory, based on the fact that patients with epilepsy suffer

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Table 1
Comparison of stimulation strategies to improve cognition in humans.

	Target	Amplitude	Frequency (Hz)	Pulse width (μs)	Clinical improvement
Suthana et al [15]	Entorhinal cortex	Approximately 0.5–1.5 mA	50 (5-s cycles)	300	Six patients with epilepsy with shorter latency and less excess path length[a]
Laxton et al [24]	Fornix within hypothalamus	Approximately 3.0–3.5 V	130	90	Four patients with dementia (among six) below expected decline in ADAS-cog
Marshall et al [18]	Frontolateral cortex	0.517 $mAcm^{-2}$	0.75	—	Thirteen health participants with enhanced declarative memory

ADAS-cog = Alzheimer's Disease Assessment Scale, Cognitive Subscale.
[a] Participants undergoing simulation: spatial learning task.

anterograde amnesia while preserving previous explicit memory after surgery to remove the bilateral hippocampus and surrounding neurons [7–9]. Advances in brain imaging and electrophysiology have also provided evidence and the mechanisms by which these areas are involved during the cognitive process. Bartolomei et al first demonstrated that entorhinal cortex (EC) stimulation is more often associated with *déjà vu* or context-specific memories compared with the perirhinal cortex, amygdala, or hippocampus [10]. This concept was further exemplified in another group of patients with epilepsy in whom depth electrode stimulation within the temporal lobe evoked autobiographical memory [11]. Taken together, the activation of large neural networks from the amygdala and hippocampus to the rhinal cortex seems to be a prerequisite to retrieve recent or remote memory.

Given the importance of medial temporal structures including the hippocampus and EC in memory encoding, these areas have been under vigorous investigation [5]. In the beginning, electrical stimulation of the perforant pathway, which originates in the EC and projects into the hippocampus, showed memory improvement via long-term potentiation, acetylcholine release, and theta-phase resetting in rats [12,13]. Furthermore, facilitation of working spatial memory has been proved when the EC is stimulated during the learning phase. Suthana et al convincingly demonstrated positive results of spatial navigation enhancement in humans (patients with epilepsy) when stimulation was applied over the EC in patients learning spatial landmarks [14,15]. Resetting of theta rhythms as power increases after electrical stimulation is considered the electrophysiological mark for this short-term learning [16].

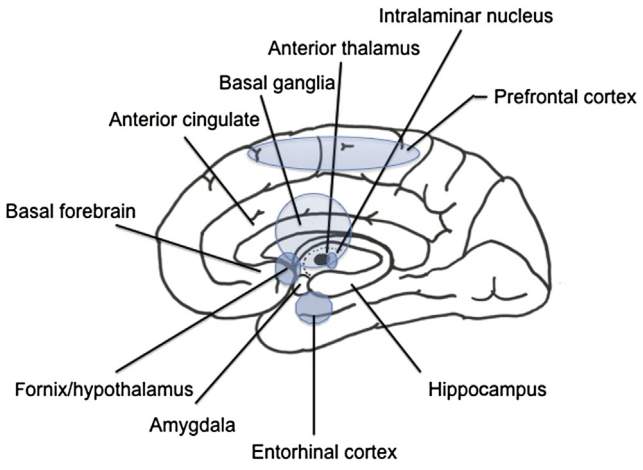

Fig. 1. Brain structures implicated to be involved in memory circuits and potential targets to enhance cognitive function.

2.2. Transcranial stimulation potentiates memory consolidation

Neuronal oscillations within cortical networks have been associated with functionally relevant cognition [17]. Slow oscillation with peaks at approximately 0.7–0.8 Hz, best characterized during slow-wave sleep, is postulated to synchronize with neocortical activity and contributes to the establishment of thalamic and hippocampal circuitries. Through application of slow oscillating-like potential fields (0.75 Hz) by transcranial direct current stimulation (tDCS) during nocturnal nonrapid-eye-movement sleep, retention of hippocampus-dependent declarative memory in humans can be enhanced [18]. Most previous translational studies have tried to explore cognitive improvement based on clinically applicable DBS parameters [3]. The field effect created over the cortical extracellular space by tDCS not only allows probing of brain rhythms during the intellectual process, but also provides a valuable, noninvasive tool to facilitate memory function that is modulated by low and harmonious oscillation [19,20].

2.3. Fornix/hypothalamic DBS in AD

Most studies probing the neural basis of learning and memory in humans rely on patients with epilepsy who have had implantation of surgical electrodes to record and stimulate the brain to identify epileptic foci [21]. However, little is understood about how these methods and findings can be replicated in AD, which is characterized by impairments in neural structures and connections underlying learning and memory. Recently, modulation of the pathological circuit in AD with DBS has been shown to increase glucose metabolism in the temporal and parietal lobes where memory circuits are involved [22]. This 1-year phase I trial was conducted based on a serendipitous finding of induction of autobiographical memory recall (*déjà vu*) after implantation of fornix/hypothalamus DBS in a morbidly obese patient [23]. In this case report, the activation of the hippocampus and medial temporal lobe in electroencephalography also correlated with this reversible cognitive episode.

To further explore the benefits of DBS for memory-impaired patients, Laxton et al followed six patients with mild AD who had undergone fornix/hypothalamus DBS for 1 year. The results showed that the progressive decline characteristic of AD could be improved or slowed [24]. Specific activation of the posterior cingulate and medial parietal lobe physiologically, and metabolic reversal of reduced cortical glucose utilization in the temporal and parietal lobes in patients with AD provide the underpinning of

how DBS might potentiate the therapeutic effects on memory impairment.

3. Proposed neural mechanism of action underlining cognitive improvement

3.1. Spatial- and temporal-specific stimulation: EC stimulation

DBS has been proved to enhance spatial learning memory in both rodents and humans. Furthermore, this kind of effect is event related. Neural excitability can be fine-tuned by activity-dependent plasticity, which manifests as reorganization or relocation of subcellular structures [25]. Two studies of entorhinal stimulation to enhance spatial memory indicate the importance of application during the learning phase, when recruitment of cognitive circuits and plasticity formation are demanded most [26,27]. It has been suggested that the efficacy of neural connections is strengthened when there is a persistent causal relationship between presynaptic and postsynaptic activity and such activity-dependent plasticity may underlie the reorganization or cortical representation during learning. All these *in vivo* findings highlight the use of phase-orientated stimulation from neuroprosthetic devices to improve cognition, instead of continuous use for movement or psychiatric disorders. Future studies are necessary to compare the effectiveness of stimulation applied at different stages of the memory process, from learning, encoding, and storing to retrieval.

3.2. Widespread activation of the cognitive circuit—fornix/hypothalamus stimulation

Although the precise mechanism of fornix/hypothalamus stimulation is unknown, preferential axonal activation within the fornix in turn provokes widespread downstream primary and secondary connected structures, including the impaired default mode network in AD [22]. In addition, impairment of memory recollection attributed to a damaged fornix suggests its pivotal role within the cognitive circuit [28,29]. These findings are consistent with a number of animal studies showing that the hypothalamic stimulation may modulate memory function and suggest that stimulation of other areas within the limbic pathway may induce selective long-term memory recall [30]. What needs to be further elucidated from this study might be target and stimulation paradigms. Although stimulation is claimed to activate the Papez circuit, which is implicated in storing memory, whether the fornix, hypothalamus, or mammillothalamic tract alone or together are responsible for the effects on verbal memory enhancement remains to be determined. Furthermore, we are uncertain to what extent continuous stimulation could be beneficial for circuit plasticity or activity-dependent effects according to the cognitive demand. Through exploration of brain-stimulating effects in animals with dementia, we might provide optimal parameters and target selection for humans with memory impairment [31].

3.3. Enhanced neurogenesis incorporates into the cognitive circuit

Stone et al found that neurogenesis of the dentate gyrus and subsequent recruitment of these “new neurons” within hippocampal circuits underlie this cognitive augmentation [14]. Interestingly, formation of specific spatial navigation in mice (water maze memory in this study) could only be improved at 6 weeks rather than at 1 week after stimulation of the EC. These delay-dependent effects explained why adult-generated dentate granule cells are required to mature and integrate into dentate circuits supporting water maze memory. A few studies involving direct electrical stimulation of the hippocampus in rodents and humans have shown disappointing results or even a negative impact on subsequent memory acquisition [32,33].

Anterior thalamus (AT) DBS has recently been under investigation for cognitive improvement owing to its cortical activation in patients with epilepsy [34,35]. When rodents were given AT DBS directly connected with the hippocampus, modulation of hippocampal neurons and increased neurogenesis, which were previously suggested to correlate with cognitive performance, could be achieved [36,37]. In addition, recruitment of newly formed neurons implicated in the cognitive process also indicated the importance of the duration of stimulation in ensuring long-term plasticity [38].

4. Conclusions

The heterogeneity of dementia indicates that its origins may lie in dysfunction of multiple brain regions. The development of novel treatments for dementia is predicted based on the identification of neural substrates and mechanisms that underlie its pathophysiology. Brain stimulation implemented directly or indirectly has emerged as an alternative treatment for specific contexts of memory function in patients and healthy humans. Our understanding of how brain stimulation works as well as comprehensive elucidation of individual parameters physiologically might decode the memory process and attenuate the dysfunctional status in patients.

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